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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,502	05/18/2001	Michel Sadelain	MSK.P-040	1539

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OPPEDAHL AND LARSON LLP
P O BOX 5068
DILLON, CO 80435-5068

EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	19

DATE MAILED: 12/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,502	SADELAIN ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *7-11 and 21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,12-20 and 25 -32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Notice to comply w Raw Sequence Listing Error Summary

DETAILED ACTION

1. The amendment filed Sep. 8, 2003 is acknowledged. Applicants' remarks with regard to the propriety of the restriction requirement are noted, and claims to the nucleic acid product, host cells and expression vectors will be examined with claims to the protein product. However, claims directed to methods of use remain restricted, because the nucleic acid and protein products are obvious over the prior art. Therefore, the nucleic acid and protein products are not considered "special technical features" that define a contribution made over the prior art (MPEP, T-48, Rule 13, section 13.2).

2. Claims 1-32 are pending.

Claims 7-11, and 21-24,drawn to non-elected inventions, are withdrawn from consideration.

Claims 1-6, 12-20 and 25-32 are examined on the merits.

Claim Rejections Withdrawn:

3. The rejection of claim 1 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment.

4. The rejection of claims 3-5, and 18-20 under 35 U.S.C. 112, first paragraph, for lack of enablement commensurate with the scope of the claims, is withdrawn in view of the amendment to the claims.

Claim Rejections Maintained:

5. The objection to the specification for not complying with the sequence rules is maintained. The Electronic Filing System submission of the sequence listing contains errors that could not be corrected by STIC. A Raw Sequence Listing Error Report is included with this Office action.

This application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant is given the time period for reply to this office action within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136. In no case may an applicant extend the period for response beyond the six-month statutory period. Applicant is requested to return a copy of the attached Notice to Comply with the response.

6. The rejection of claims 4 and 19 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention is maintained for the reasons of record, and applied to claims 27 and 31.

Claim 4 is indefinite because it refers to specific amino acid residues without a reference a specific amino acid sequence having a sequence identifier. Applicants argue that one of skill in the art would not have difficulty in determining the scope of claim 4 (and therefore 19, 27 and 31, which depend from claim 4) because the sequence of CD28 is known. This argument is not found persuasive because the reference referred to by applicant is not incorporated by reference in the application, and furthermore, it is not clear if the CD28 sequence referred to by applicants is the only one known in the art, or if there are other versions. By referring to specific bases in the claim, the claim appears to be of narrow scope, i.e., that perhaps only one species of CD28 cDNA is referred to, but by also using a broader term in conjunction with a reference to a specific sequence, the meaning of the claim is not clear, and the scope of the claim cannot be determined.

7. The rejection of claims 1-4 under 35 U.S.C. 103(a) as being unpatentable over Eshhar et al (US 2002/0137697; published 09/2002; filed 10/1995) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998) and further in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995) is maintained for the reasons of record. This rejection is applied to claims 13 and 29-31, which are drawn to expression vectors comprising nucleic acids that encode the constructs of claims 1-4, and also to claims 12 and 25-27, which are drawn to host cells comprising the expression vectors, wherein the host cells are peripheral blood lymphocytes (PBL).

Applicants' remarks with regard to the propriety of using Eshhar (US 2002/0137697) are noted. However, the MPEP states that under the current version of 102(e), which may be relied upon as the basis of a rejection under 103(a), the filing date of the application is not relevant to the analysis of whether a reference may be used as prior art. See MPEP 2136:

> ***>Revised 35 U.S.C. 102(e), as amended by the American Inventors Protection Act of 1999 (AIPA) (Pub. L. 106-113, 113 Stat. 1501 (1999)), and as further amended by the Intellectual Property and High Technology Technical Amendments Act of 2002 (Pub. L. 107-273, 116 Stat. 1758 (2002)), applies in the examination of all applications, whenever filed, and the reexamination of, or other proceedings to contest, all patents. Thus, the filing date of the application being examined is no longer relevant in determining what version of 35 U.S.C. 102(e) to apply in determining the patentability of that application, or the patent resulting from that application. The revised statutory provisions supercede all previous versions of 35 U.S.C. 102(e) and 374, with only one exception, which is when the potential reference is based on an international application filed prior to November 29, 2000 (discussed further below). The provisions amending 35 U.S.C. 102(e) and 374 in Pub. L. 107-273 are completely retroactive to the effective date of the relevant provisions in the AIPA (November 29, 2000). Revised 35 U.S.C. 102(e) allows the use of certain international application publications and U.S. patent application publications, and certain U.S. patents as prior art under 35 U.S.C. 102(e) as of their respective U.S. filing dates, including certain international filing dates. The prior art date of a reference under 35 U.S.C. 102(e) may be the international filing date if the international filing date was on or after November 29, 2000, the international application designated the United States, and the international application was published by the World Intellectual Property Organization (WIPO) under the Patent Cooperation Treaty (PCT) Article 21(2) in the English language. See MPEP § 706.02(f)(1) for examination guidelines on the application of 35 U.S.C. 102(e).<*

Eshhar teaches chimeric receptors that comprise an scFv that binds a tumor antigen connected to a cytoplasmic domain such as that of a ζ-chain of CD3, or a cytoplasmic domain of CD28 (see page 3, para. 24; para. 19; page 2, para. 17 ; page 11, para. 99). Between the scFv

and the cytoplasmic domain is a transmembrane domain, which is interpreted to be a linker (page 1, para 7). Thus, Eshhar teaches constructs that have an scFv that binds a tumor antigen linked to a cytoplasmic domain via a linker. Eshhar teaches peripheral blood lymphocytes transduced with vectors encoding chimeric receptors (para 119-126).

Eshhar fails to teach a chimeric receptor having an scFv that binds PSMA. However, antibodies to PSMA are known in the art and hybridomas expressing PSMA antibodies are readily available as taught by Murphy I (col. 6). Furthermore, the suggestion to make chimeric receptors that target PSMA is also found in the art; Murphy II teaches that PSMA is a useful target for immunological methods of treatment (see col. 3, lines 41-47). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the chimeric receptors of Eshhar to comprise an scFv that binds PSMA. One would have been motivated to make such a modification because PSMA has been taught to be a cancer antigen and a target for immune system therapies.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, Eshhar teaches the general concept of combining the targeting features of an scFv directed to a tumor antigen with an immune cell triggering moiety, such as a cytoplasmic domain of CD3 or CD28. Because PSMA is known in

the art to be a useful target for immunological methods, as taught by Murphy II, it would be obvious to use the scFv of Murphy I in combination with the constructs of Eshhar to make the claimed inventions.

8. The rejection of claims 1-4, 6, and 17-19 under 35 U.S.C. 103(a) as being unpatentable over Eshhar et al (US 2002/0137697; published 09/2002; filed 10/1995) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995) and further in view of Darcy et al (Darcy, P.K. et al., Eur. J. Immunol. 28: 1663-1672, 1998; cited in the IDS) is maintained for the reasons of record, and applied to claims 12, 13, 25-27, and 29-31, drawn to host cells and expression vectors.

Claims 1-4, 6, 12, 13, 17-19, 25-27 and 29-31 may be interpreted to read on fusion receptors having a connector, where the connector is a CD8 hinge, and expression vectors comprising nucleic acids encoding said fusion receptors. The combination of Eshhar, Murphy I and Murphy II fails to teach fusion receptors comprising a linker that is a CD8 hinge. However, using the CD8 hinge in a chimeric T cell receptor construct is known in the art as shown by the teachings of Darcy, which teaches a fusion receptor comprising an anti-CEA scFv linked to transmembrane and cytoplasmic regions of the human FcγR chain, with a CD8 hinge in between the scFv and transmembrane and cytoplasmic regions of FcγR chain. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a linker that is a CD8 hinge.

In response to applicants' arguments that there is no motivation to use the CD8 hinge of Darcy with the construct of Eshhar, applicants' attention is directed to page 1664, 1st column, in which Darcy teaches that the inclusion of the CD8 hinge allows optimal binding of the CEA antigen to the anti-CEA scFv component of the fusion receptor.

9. The rejection of claims 1-4 under 35 U.S.C. 103(a) as being unpatentable over Capon et al (US 5,359,046; issued 10/1994; filed 12/1992) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998) and further in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995) is maintained for the reasons of record, and applied to claims 12 and 29-31.

Capon teaches chimeric proteins, and vectors comprising DNA that encode such proteins, that comprise an scFv that binds a tumor antigen that is linked to transmembrane domain that is linked to a cytoplasmic domain. Thus, Capon teaches chimeric proteins that comprise a linker between the scFv and the cytoplasmic domain. Capon fails to teach a chimeric protein having an scFv that binds PSMA. However, antibodies to PSMA are known in the art and hybridomas expressing PSMA antibodies are readily available as taught by Murphy I (col. 6). Furthermore, the suggestion to make chimeric receptors that target PSMA is also found in the art; Murphy II teaches that PSMA is a useful target for immunological methods of treatment (see col. 3, lines 41-47). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the chimeric receptors of Capon to comprise an scFv that binds PSMA. One would have been motivated to make such a modification because PSMA has been taught to be a cancer antigen and a target for immune system therapies.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, Capon teaches the general concept of combining the targeting features of an scFv directed to a tumor antigen with an immune cell triggering moiety, such as a cytoplasmic domain of T-cell receptors. Because PSMA is known in the art to be a useful target for immunological methods, as taught by Murphy II, it would be obvious to use the scFv of Murphy I in combination in the constructs of Capon to make the claimed inventions.

10. The rejection of claims 1-4, 6, and 17-19 under 35 U.S.C. 103(a) as being unpatentable over Capon et al (US 5,359,046; issued 10/1994; filed 12/1992) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995) and further in view of Darcy et al (Darcy, P.K. et al., Eur. J. Immunol. 28: 1663-1672, 1998; cited in the IDS) is maintained for the reasons of record and applied to claims 12 and 29-31.

The combination of Capon, Murphy I and Murphy II fails to teach fusion receptors comprising a linker that is a CD8 hinge. However, using the CD8 hinge in a chimeric T cell receptor construct is known in the art as shown by the teachings of Darcy, which teaches a fusion

receptor comprising an anti-CEA scFv linked to transmembrane and cytoplasmic regions of the human FcγR chain, with a CD8 hinge in between the scFv and transmembrane and cytoplasmic regions of FcγR chain. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a linker that is a CD8 hinge.

In response to applicants' arguments that there is no motivation to use the CD8 hinge of Darcy with the construct of Capon, applicants' attention is directed to page 1664, 1st column, in which Darcy teaches that the inclusion of the CD8 hinge allows optimal binding of the CEA antigen to the anti-CEA scFv component of the fusion receptor.

11. The rejection of claims 1 and 5 under 35 U.S.C. 103(a) as being unpatentable over either Eshhar et al (US 2002/0137697; published 09/2002; filed 10/1995) or Capon et al (US 5,359,046; issued 10/1994; filed 12/1992) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995) and further in view of Alderson et al (Alderson et al, Eur. J. Immunol, 24(9): 2219-2227, 1994; abstract only) is maintained and applied to claims 13, 28 and 32.

Neither Eshhar nor Capon teaches cytoplasmic domains that are the 4-1BB cytoplasmic domain. However, both Eshhar and Capon teach generally that cytoplasmic domains may be the cytoplasmic domains of T-cell receptors. Alderson teaches that 4-1BB is a T cell receptor and teaches the DNA sequence. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a fusion receptor comprising a 4-1BB cytoplasmic domain. The motivation for using the 4-1BB cytoplasmic domain is found in

the teachings of either Eshhar or Capon, which teach that the cytoplasmic domains of T cell receptors are useful in making chimeric T-cell receptors.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, either Eshhar or Capon teaches the general concept of combining the targeting features of an scFv directed to a tumor antigen with an immune cell triggering moiety, such as a cytoplasmic domain of T-cell receptors. Because 4-1BB is known in the art to be T-cell receptor, it would be obvious to use it in the constructs of either Eshhar or Capon to make the claimed inventions. Furthermore, applicants' have failed to show that the prior art teaches away from using the $-1BB cytoplasmic domain or that applicants' have observed unexpected results in the making of chimeric receptors comprising a 4-1BB cytoplasmic domain.

12. The rejection of claims 1, 5, and 20 under 35 U.S.C. 103(a) as being unpatentable over either Eshhar et al (US 2002/0137697; published 09/2002; filed 10/1995) Capon et al (US 5,359,046; issued 10/1994; filed 12/1992) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995), in view of Darcy et al (Darcy, P.K. et al., Eur. J.

Immunol. 28: 1663-1672, 1998; cited in the IDS), and further in view of Alderson et al (Alderson et al, Eur. J. Immunol, 24(9): 2219-2227, 1994; abstract only) is maintained and applied to claims 13, 28and 32.

Claims 1, 5 and 20 may be interpreted to read on chimeric receptors that comprise both a CD-8 hinge and a 4-1BB cytoplasmic domain. As discussed above, the combination of either Eshhar or Capon with Murphy I, Murphy II and Alderson teaches a chimeric receptor that comprises a 4-1BB cytoplasmic domain. However, the combination fails to teach the use of CD-8 hinge. However, Darcy teaches the benefits of using a CD-8 hinge in the construction of a chimeric receptor. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have made a chimeric receptor that comprised both a CD-8 hinge and a 4-1BB cytoplasmic domain.

In response to applicants' arguments, as discussed above, the advantages of using a CD-8 hinge are known in the art as evidenced by the teachings of Darcy. Therefore, one of ordinary skill in the art would have been motivated to use the CD-8 hinge in the construction of a chimeric receptor.

New Grounds of Rejection:

13. Claims 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed

invention. The basis for this rejection is that the specification lacks a definition and description of the SFG vector, which are necessary for the practice of the inventions of claims 14 and 15.

Claims 13 and 14 are drawn to expression vectors comprising a polynucleotide sequence encoding a chimeric fusion receptor of claim 1, wherein the expression vector is an SFG vector. The specification refers to a paper for the description of the SFG vector. However, upon review of the reference (Riviere et al, PNAS, 92: 6733-6737, 1995), there does not appear to be a description or reference to an SFG vector. Therefore, the claimed inventions lack written description, and one of skill in the art would not find that applicant was in possession of the claimed inventions at the time the application was filed.

14. Claims 14 and 15 are objected to for reciting an abbreviation without first setting forth the entire name of the term. Specifically, the term SFG appears to be an abbreviation that is not defined.

15. Claims 13 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Eshhar et al (US 2002/0137697; published 09/2002; filed 10/1995) or Capon et al (US 5,359,046; issued 10/1994; filed 12/1992) in view of Murphy et al ("Murphy I", U.S. Patent 6,383,759; issued 05/2002; filed 05/1998), in view of Murphy et al ("Murphy II", U.S. Patent 5,788.963; issued 08/1998; filed 07/1995), and further in view of Gallardo (Gallardo, H.F. et al, Blood, 90: 952-957, 1997; cited in the IDS).

Claims 13 and 16 are drawn to expression vectors encoding chimeric fusion receptors where the expression vector is packaged in gibbon ape leukemia virus (GaLV) enveloped

pseudotyped virions. The combination of Eshar or Capon with Murphy I and Murphy II teach expression vectors encoding a chimeric fusion receptor that is packaged into retrovirus particles for transfection. The combination fails to teach the specific virus that is gibbon ape leukemial virus. However, Gallardo teaches the use of such viruses for transfection into primary T lymphocytes, and that virus particles psuedotyped with he GaLV envelope are far more infectious on a particulate basis than the vesicular stomatisitis virus. Therefore, it would have been obvious to one of ordinary skill in the art to have modified the teachings of either Eshhar or Capon by using GaLV envelope pseudotype virions as taught by Gallardo. One would have been motivated to use the teachings of Gallardo because of the high efficiency of gene transfer achievable with such constructs.

Conclusion

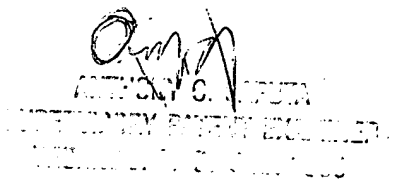
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
December 29, 2003



Notice to Comply With Sequence Rules	Application No.	Applicant(s)	
	09/786,502	SADELAIN ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

X 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 8230, May 1, 1990.

___ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

X 3. A copy of the "Sequence Listing" in Computer Readable Form (CRF) has not been submitted as required by 37 C.F.R. 1.821(e).

X 4. A copy of the "Sequence Listing" in Computer Readable Form (CRF) has been submitted. However, the content of the CRF does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

___ 5. The Computer Readable Form (CRF) that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute CRF must be submitted as required by 37 C.F.R. 1.825(d).

___ 6. The paper copy of the "Sequence Listing" is not the same as the Computer Readable Form (CRF) of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

___ 7. Other: _____

Applicant Must Provide:

X An initial or substitute copy of the **CRF** "Sequence Listing".

___ An initial or substitute **paper copy** of the "Sequence Listing", as well as an amendment directing its entry into the specification.

___ A statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support (SIRA)
Technical Assistance.....703-287-0200
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